MOLECULAR RECOGNITION OF CARBAMAZEPINE POLYMORPH

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SUPERVISOR'S DECLARATION

"I hereby declare that I have checked this thesis and in my opinion, this thesis is adequate in terms of scope and quality for the award of the degree of Bachelor of Chemical Engineering".

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STUDENT'S DECLARATION

I hereby declare that the work in this thesis is my own except for quotations and summaries which have been duly acknowledged. The thesis has not been accepted for any degree is not concurrently submitted for award of other degree.

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Special dedication to my supervisor, my family members,
my friends, my fellow colleague and all faculty members
for all your care, support and believe in me.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS

t	Time
D	Diffusion coefficient
C	Concentration
g (r)	Radial distribution function
r	Radius
ρ	Density
N	Number of molecules

MENGENALPASTI MOLEKUL POLIMORF CARBAMAZEPINE

ABSTRAK

Penyelidikan ini adalah mengenai simulasi molekul dinamik carbamazepine dengan menggunakan perisian material studio.Dalam kajian ini, untuk bahagian eksperimen menggunakan dua jenis pelarut iaitu etanol, dan aseton untuk melihat kesan pelbagai jenis pelarut ke arah bentuk Polimorf dan pembentukan interaksi dan etanol hanya digunakan untuk simulasi disebabkan beberapa masalah berlaku semasa kajian ini. Objektif kajian ini adalah untuk mengkaji kesan pelbagai pelarut pada kristal carbamazepine. Simulasi molekul dinamik dilakukan menggunakan Studio Material untuk etanol dan carbamazepine dengan menggunakan COMPASS Field Force bersama-sama dengan Modul Forcite dan Amourphous. Dinamik yang dijalankan untuk pelarut tulen dilakukan pada mulanya dalam ensemble NVE pada 200 ps dan diikuti oleh NPT ensemble pada 100-200 ps. Bahagian eksperimen, jumlah jisim carbamazepine dicampurkan bersama-sama dengan jumlah 3ml isipadu pelarut sehingga terdapat lebihan CBZ dan dianalisis dengan FTIR. Dari fail trajektori, kepadatan, fungsi taburan jejarian (RDF) dan pekali resapan dianalisis dan dikira. Ia dijangka bahawa simulasi MD dapat mengaitkan RDF dengan kumpulan tertentu berfungsi dalam struktur pelarut. Berdasarkan pada RDF, Berdasarkan kepada rdf, kebarangkalian untuk mencari interaksi antara molekul khususnya ikatan hidrogen yang merupakan satu bentuk tarikan yang agak kuat antara molekul dalam pelarut tertentu boleh dinilai. Ia adalah sejenis daya tarikan antara molekul yang wujud di antara dua cas separa elektrik yang bertentangan kekutuban.Ia adalah sejenis daya yang menarik molekul yang wujud di antara dua tuduhan separa elektrik kekutuban yang bertentangan. Perbezaan interaksi atom dari trend RDF menunjukkan bahawa jenis penggunaan pelarut dalam proses penghabluran carbamazepine boleh membawa kepada polymorphism.

MOLECULAR RECOGNITION OF CARBAMAZEPINE POLYMORPH

ABSTRACT

The research is about the molecular dynamic simulation of carbamazepine by using the material studio software. In this research, for the experimental section we used two types of solvent that is ethanol, and acetone to observe the affect of the different types of solvent toward the polymorphs form and the formation of the H-bond and only ethanol used for simulation due to several problem occurs during this research. The objective of this research is to study the effect of various solvents on carbamazepine crystal. MD simulation is performed using Material Studio for ethanol and carbamazepine by applying COMPASS Force Field together with Forcite and Amourphous Cell Module. The dynamics run for pure solvent is performed initially in NVE ensemble at 200 ps and followed by NPT ensemble at 100-200 ps. The experimental section, amount mass of carbamazepine mixed together with 3ml volume of different types of solvent until excess appeared and analysis with FTIR. From the trajectory files, the density, radial distribution function (rdf) and diffusion coefficient were analyzed and calculated. It is expected that MD simulation able to correlate rdf with the specific functional group in solvents structure. Based on the rdf, the probabilities of finding specific intermolecular interactions of hydrogen bond which is a relatively strong form of intermolecular attraction in specific solvents can be assessed same goes to experimental result which shows different trend H-bond formed by using different types of solvent. It is a type of attractive intermolecular force that exists between two partial electric charges of opposite polarity. The difference atomic interaction from the rdf trends show that the type of solvent use in carbamazepine crystallization process may lead to the polymorphism.

CHAPTER 1

INTRODUCTION

This chapter provide the general ideals on the subject that are going to be study including background of proposed study, problem statement, research objectives, scope of proposed study, expected outcome and significance of proposed study.

1.1 Background of Proposed Study

In the last decades, it has been proved that once a compound with pharmacological applications is developed, the characterization of its solid state is one of the most important stages for the development of the pharmaceuticals. An

appropriate characterization is needed since solid pharmacological forms can be presented as different polymorphs, solvates or amorphous forms, which generally have different bioavailabilities and clinical use.

Polymorphism is the crystallization of the same compound in more than one distinct crystal architecture and is associated with different crystal packing arrangements. This phenomenon is very common in pharmacological drugs, as it is the case of carbamazepine (5H-dibenz(b,f)-azepine-5-carboxamide). This drug whose chemical formula is $C_{15}H_{12}N_2O$ has been in routine use in the treatment of epilepsy and trigeminal neuralgia for over 30 years. There are different polymorphic forms have been confirmed for the anhydrous carbamazepine that is form III, the commercial one, form I, and form II and certain analytical results suggest the existence of additional forms and the formation of mixed crystals. In spite of possessing the same active part or molecule, polymorphs have different chemical and physical properties such as they have different melting points, different chemical reactivity, different dissolution rates, and different bioavailability and the polymorph III of carbamazepine is the only one that has desirable therapeutic effects.

1.2 Problem Statement

Polymorphism and solvate formation represents a major issue in pharmaceutical crystallization to pharmaceutical industry and in terms of patent establishment and protection, reliability of production, and stability on storage and in

processing. Methods of studying the structure and properties of polymorphs and solvates are therefore of paramount importance. Different types of solvent used will affect the interaction between the solute-solvent and how do solute-solvent interact to reflect the polymorphism due to the different solubility.

1.3 Research Objectives

The research objective of this study is:

1) To study the effect of solvent types on carbamazepine crystal polymorph from the crystallization process.

2) To investigate the correlations in the inter-atomic distances between specified atoms on solute molecules by determine
    i) Time-averaged rdf calculated from MD simulations
    ii) Check the dimer (H-bond) exists in crystal & solution.

1.4 Research Questions/Hypothesis

The research questions of this study is to know what is the relation between the solute-solvent intermolecular interactions in different types of solvent to be used and the relation between inter-atomic distances between specified atoms on solute molecules that is carbamazepine.

1.5 Scope of Proposed Study

The scopes of this study is focusing on the crystallization polymorph of Carbamazepine in solute-solvent interaction and the inter-atomic distances between specified atoms on solute molecules by determine their time-averaged and the presence of H-bond in the crystal structure and solutions. Also includes the relation, time-averaged, probability of forming specific solute-solute versus specific solute-solvent intermolecular interactions in different types of solvent at the specific number of 300 solvent and 100 solutes at room temperature, 25 °C.

1.6 Expected Outcome

The expected outcome of this study is to clearly understand on how the solute-solvent interaction influence the crystallization and how different solvent used affected the solubility of the carbamazepine by examined the time-averaged of the solute-solvent interactions and the existence of H-bond in the crystal and solutions.

1.7 Significance of Proposed Study

The significance of this study is to modelling a simulation as a major pharmaceutical industry ways to use the predictive science to reduce cost and time in research and development especially in pharmaceutical field which is then compared with experimental. In addition, the understanding of polymorphism should be understood of the molecular level. This is to help an engineer to be able to manipulate the molecular properties to obtain the desired product quality.

1.8 Concluding Remark

As a conclusion, the use of simulation plays an important role especially in pharmaceutical industry which helps the researcher to do the research with save time and low cost because they don’t have to set up the real experiment and just need to create the model like the real process or system in computer in order to achieve their objective while run the experiment by simulation and the simulation result can be compared to experimental results.

CHAPTER 2

LITERATURE REVIEW

This chapter provide the general ideals on the subject that are going to be study including the background and introduction of molecular dynamic simulation of carbamazepine, definition of this topic, factor influences the study and the properties of each compound used in this study.

2.1 History and Background of Molecular Dynamic Simulation

Molecular dynamics simulation techniques are widely used in experimental procedures such as X-ray crystallography and NMR structure determination. The molecular dynamics method is the study of the interactions of hard spheres. (Alder and Wainwright, 1957,1959). Many important insights concerning the behavior of simple liquids emerged from their studies. The next major advance was in 1964,

when Rahman carried out the first simulation using a realistic potential for liquid argon (Rahman, 1964).

The first molecular dynamics simulation of a realistic system was done by Rahman and Stillinger in their simulation of liquid water in 1974 (Stillinger and Rahman, 1974). Today in the literature, one routinely finds molecular dynamics simulations of solvated proteins, protein-DNA complexes as well as lipid systems addressing a variety of issues including the thermodynamics of ligand binding and the folding of small proteins. The first protein simulations appeared in 1977 with the simulation of the bovine pancreatic trypsin inhibitor (BPTI) (McCammon, et al, 1977).

The importance of the simulation tools that are capable of tracking equipment utilization for overlapping batches that can identify the bottleneck candidates, guide the user through the debottlenecking effort and act as a major pharmaceutical industry ways to use the predictive science method to reduce cost in research and development cost rather than save the time without run the real experiment. Environmental issues not addressed during process development may lead to serious headaches during manufacturing. This is the case because after a process has been approved by the regulatory agencies, it is extremely costly and time-consuming to make process changes and this is particularly true especially for biopharmaceuticals field (Petrides et al., 2002).

2.2 Molecular Dynamic Simulation

Molecular Dynamics is a form of computer simulation where atoms and molecules are allowed to interact for a period of time under known laws of physics or defined as the operation of a model of the system to evaluate the performances of a system, existing or proposed, under different configuration of interest and over long periods of real time and used to investigate the structure, dynamics and thermodynamics of materials and biological systems. It can be classified as computer experiment that can provide the test of a new theoretical result (Frenkel et al., 2002).

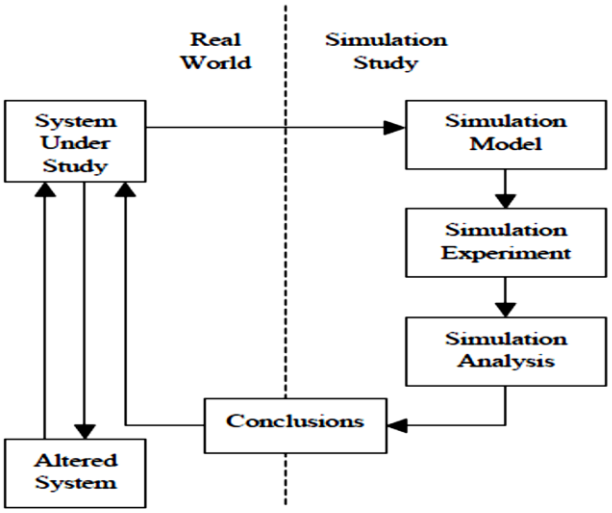


Figure 2.1 Simulation Study Schematic

(Source: Maria, 1997)

Figure 2.1 shows a schematic of a simulation study. The iterative nature of the process is indicated by the system under study becoming the altered system which then becomes the system under study and the cycle repeats (Maria, 1997).

In a simulation study, human decision making is required at all stages, namely, model development, experiment design, output analysis, conclusion formulation, and making decisions to alter the system under study. The only stage where human intervention is not required is the running of the simulations, which most simulation software packages perform efficiently. The important point is that powerful simulation software is merely a hygiene factor, its absence can hurt a simulation study but its presence will not ensure success. Experienced problem formulators and simulation modelers and analysts are indispensable for a successful simulation study. Although this is a logical ordering of steps in a simulation study, much iteration at various sub-stages may be required before the objectives of a simulation study are achieved. Not all the steps may be possible for certain analysis or experiment. For an additional, few steps may have to be performed or introduce to run the simulation (Maria, 1997).

In molecular dynamics, successive configurations of the system are generated by integrating Newton's laws of motion. The result is a trajectory that specifies how the positions and velocities of the particles in the system vary with time. Newton's laws of motion can be stated as follow where first, a body continues to move in a straight line at constant velocity unless a force acts upon it. Second, force is equals to the rate of change of momentum and third is for every action there is an equal and opposite reaction. The trajectory is obtained by solving the differential equations embodied in Newton's second law,

$$F = ma : \quad \textbf{(}2.1)$$

$$\frac{d^2y}{dt^2} = \frac{F_{x_i}}{m_i} \quad (2.2)$$

This equation describes the motion of a particle of mass m_i along one coordinate (x_i) with F_{xi} being the force on the particle in that direction (Andrew, 1996).

The simulation will show the intermolecular and intramolecular interactions between the solute and solvent. This information will give the ideas on how the mass transfer behavior of the targeted molecules via the diffusion coefficient. The diffusion coefficient of the molecules can be calculated by mean square displacement at time average of simulation time. While the intermolecular forces such as hydrogen bonding will be able to describe the solvation strength of the solvent molecules towards the targeted molecules. This solvation strength of the solvent can be calculated through the calculation of the radial distribution function (RDF) (Suchoki, 2000). Radial distribution function correlated to the existence of dimers in the solution from the trajectory frames as described in the following equation:

$$g_{xy}(r) = \left[\frac{N_y\,(r,\ r+dr)}{\rho_y\ 4\pi r^2\ dr}\right] \qquad (2.3)$$

r = Spherical radius, ρ_y = density of y atom, N_y = Number atom of y

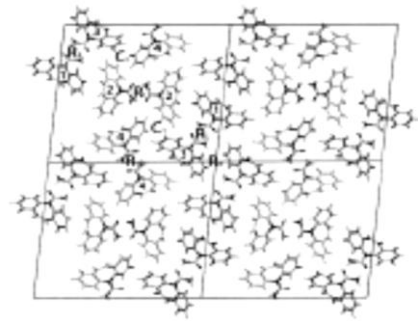
Mean square displacement will be calculate by the software using the following formula:

Mean square displacement, MSD = 6Dt + C (Rahman, 1964)

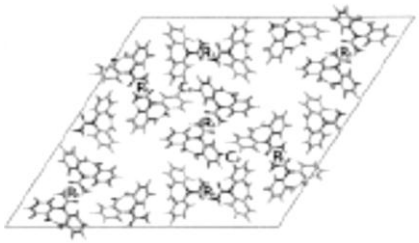
Dt = diffusion coefficient, C = Y intercept.

2.3 Carbamazepine

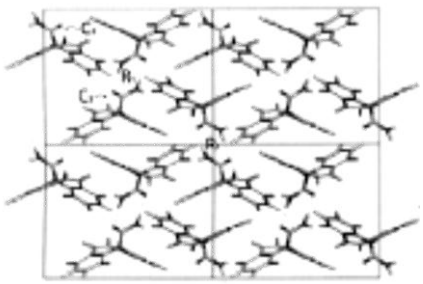
Carbamazepine is an anticonvulsant used to treat epilepsy and trigeminal neuralgia, has served as a model compound for many groups studying crystal polymorphism. This important anticonvulsant has been found to crystallize as four different anhydrous polymorphs, three of that which have been structurally characterized by single crystal X-ray diffraction. The first anhydrous polymorph was found to crystallize primitive monoclinic cell (form III), and followed by triclinic (form I), trigonal (form II), and last is C-centered monoclinic polymorph (form IV) (Grzesiak et al., 2003).



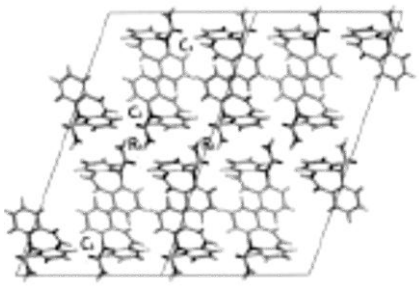
Triclinic (Form I)



Trigional (Form II)



P-monoclinic (Form III)



C-monoclinic (Form IV)

Figure 2.2 Carbamazepine hydrogen bonding patterns. (Day et al., 2005).

(Source: Day et al., 2005)

Figure 2.2 shows the packing diagram of all four form of carbamazepine hydrogen bonding patterns of carbamazepine polymorph.

Carbamazepine, 5H dibenz[b,f] azepine-5-carboxamide. This compound has found clinical use for the treatment of neuralgia and epilepsy. It is known to exist in at least four anhydrous polymorphic modifications two of which are monoclinic, one is trigonal and the final one is triclinic. The P-monoclinic form is the thermodynamically stable modification under ambient conditions. As commonly occurs in polymorphic systems, there is some confusion in the literature on the numerical numbering for these forms (Grzesiak et al, 2003).

The crystal structures of the P-monoclinic and trigonal structures have been known for over 15 years. More recently, the structure of the C-monoclinic form has been published, which was designated as a new form IV by the authors. However, this form had already been discovered in 1968 by Kuhnert-Brandsta¨tter et al. (Kuhnert-Brandstaetter, 1968) called form II, trigional and was observed later by many other authors (Krahn and Mielck, 1987).

At the time that most of the NMR work described here was carried out, the crystal structure of the triclinic form is the most stable modification at high temperature was unknown, but recently that, too, has been solved. The stability order of the four format room temperature being Pmonoclinic > triclinic > C-monoclinic > trigonal (Grzesiak et al, 2003). Thermochemical data and the densities clearly indicate an enantiotropic relationship between the P-monoclinic form and the triclinic form, and there is no doubt that the P-monoclinic form shows the lowest free

energy of all the forms at and below room temperature. From the thermochemical data evaluated it may be deduced that the C-monoclinic form and the P-monoclinic form also represent an enantiotropic pair however, the C-monoclinic and the triclinic form are monotropically related but enantiotropically related (Grzesiak et al 2003 & . Krahn and Mielck, 1987).

Table 2.1 Carbamazepine properties (Chemical Book online)

Name	Carbamazepine
Synonyms	5-Carbamoyl-5H-dibenz(b,f)azepine 5-Carbamoyldibenzo(b,f)azepine 5H-Dibenz(b,f)azepine-5-carboxamide Carbazepine Dibenz(b,f)azepine-5-carboxamide Telesmin
Molecular Weight	236.27
Solubility in water	Insoluble
Melting Point	190k – 192k
Boiling Point	411k
Appearance	Crystals from absorption in ethanol + benzene.
Density	1.296 g/cm^3
Heat Of Vaporization	66.3 kJ/mol
Usage	Medication

(Source: Chemical Book online)

2.3.1 Molecular Structure of Carbamazepine

Carbamazepine has clinical use because of its analgesic and anticonvulsant properties and is prescribed in the treatment of epilepsy and trigeminal neuralgia. X-ray structure determinations are used in pharmacological studies aimed at relating the molecular conformation of a given tricyclic drug to its physiological activity at the receptor site. In addition, accurate cell dimension and molecular parameters are needed for as it has been reported to exist in polymorphic forms (Camp, Brannon & Maienthal, 1981).

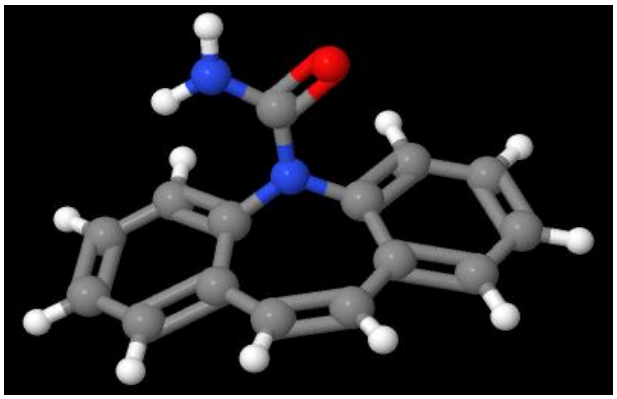


Figure 2.3 Molecular structure of Carbamazepine

(Source: http://www.chemspider.com, 2012)

Figure 2.3 shows the molecular structure of carbamazepine in 3 dimensions using ball stick model import from chemspider website.

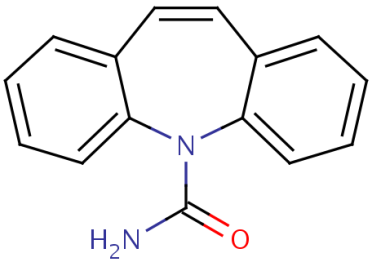


Figure 2.4 Molecular structure of Carbamazepine

(Source: http://www.chemspider.com, 2012)

Figure 2.4 shows the molecular structure of carbamazepine in 2 dimensions using frame model import from the chemspider website.

2.4 Polymorphism

Polymorphism is the ability of a substance to crystallize in a variety of different crystal structures where the presence of different structures can affect the dissolution rate, solubility, and bioavailability, among other physical characteristics (Cabeza et al., 2006). Crystal polymorphism also can be considered as importance technical in industry, especially among pharmaceutical industry in terms of patent establishment and protection, reliability of production, and stability on storage and in processing (Harris et al., 2005).

The existence of different crystal structures was reflected by the presence of the polymorphism that differs in their physicochemical properties. Different forms of

polymorphic drug may influence the pharmaceutical qualities, such as tableting characteristics, dissolution profile as well as chemical and physical stability during storage (Krahn and Mielck, 1989; Kobayashi et al., 2000; Roberts et al., 2000).

The properties of the solid material vary due to the presence of the phenomenon of crystal polymorphism. For an example, the ability of a pharmaceutical to exist as more than one crystalline polymorph, creates a situation in which one crystal form may have a favorable dissolution rate, equilibrium solubility, and absorption whereas another is an ineffective therapeutic agent. There are several factors contributing to the polymorphism such as hydrogen bonding, molecular size, and conformational flexibility (Grzesiak et al., 2003).

Despite being highly investigated, the phenomenon of polymorphism continues to present new challenges. The main factor contributing to the increase of propensity polymorphism is the hydrogen bonding and the molecular flexibility of the solid molecules (Yu et al., 1995). The conditions under which a crystal is grown clearly affect the crystal structure in polymorphic systems. The insoluble polymers have been utilized to selectively control the crystallization of one polymorph over another. The use of these polymeric heteronuclei has become an efficient and effective tool for screening for polymorphic behavior and the discovery of new polymorphs (Land et al., 2002 & Price et al., 2005).

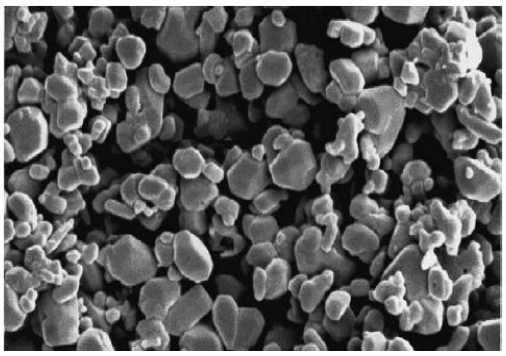


Figure 2.5 Elongated prismatic morphology of polymorph I particles of CBZ

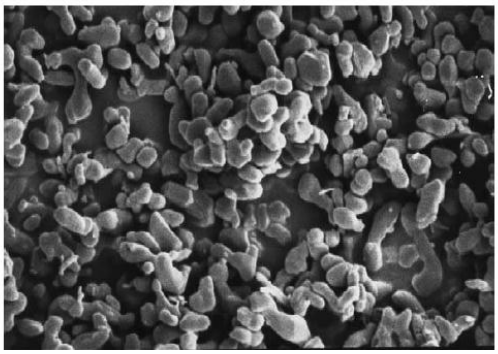


Figure 2.6 Elongated prismatic morphology of polymorph II particles of CBZ

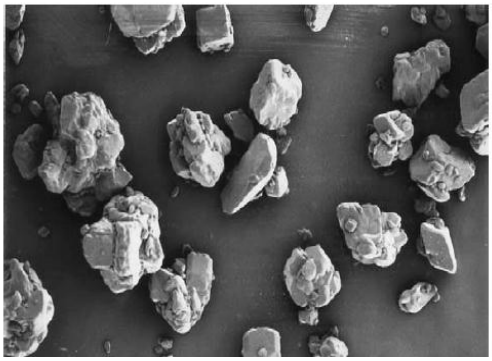


Figure 2.7 Elongated prismatic morphology of polymorph III particles of CBZ

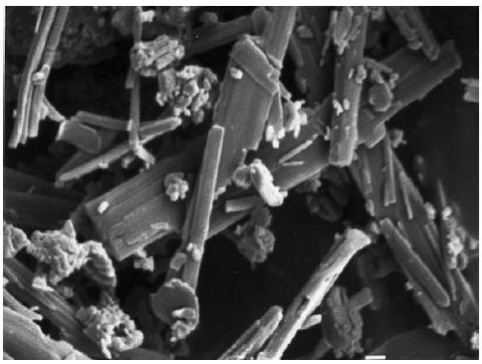


Figure 2.8 Elongated prismatic morphology of polymorph IV particles of CBZ

Figure 2.5 to 2.8 shows the photomicrograph diagram for four forms of carbamazepine polymorph produced by scanning electron microscopy under constant operating condition of 170 bar at an extraction temperature of 35 °C and an expansion temperature of 75 ◦C (5000×).

(Sources: Gosselin, P., M., et al, 2002).

2.4.1 Factor Influence the Polymorphism

Around one-third organic of organic substances show crystalline polymorphism under normal pressure conditions that is 1atm pressure (Henck et al, 1997). Stated that around 450 pharmaceutically important materials list that exhibit the polymorphism and number of factors, which affect the selectivity of different polymorphs of a given substance in crystallization processes (Borka and Haleblian, 1990).

There are several factor affect the selectivity of different polymorphs such as the type of solvent, degree of super saturation, crystallization temperature, rate of cooling, impurities and additives, surface of crystallization vessel, suspended particles, seeding and flow regime. The types of solvent are a major factor in polymorphic selectivity and also morphology due to the solvent solute interaction molecule and effect the solubility of the substance (Mirmehrabi and Rohani, 2004).

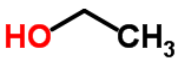
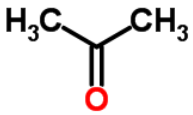
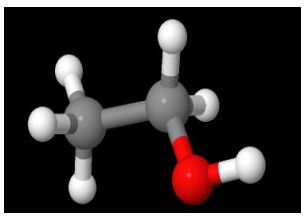
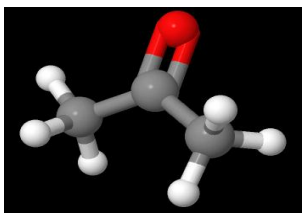
Solvent can be categorized into three categories. The first category is the hydrogen donors or polar solvent such as water and methanol, which known as dipolar protic solvents. The second category, dipolar aprotic solvents, is also polar but they are not able to donate hydrogen for bonding such as acetonitrile and nitrobenzene. The last category is the nonpolar solvents that are also aprotic such as pentane and benzene. The application of the solubility is to estimate the crystallization throughput or yield especially in cooling or anti solvent crystallizations and also for determining the thermodynamic stability regions of polymorphs because the more stable form are the form with lowest solubility.

However, the thermodynamic stability of the polymorphic systems is not a function of employed solvent and exhibits the same behavior in all solvents. If the solvent-solute is strongly bonded at a special surface, the rate-limiting step of growth is the removal of the solvent from the face. In this case the bonded surfaces grow slowly or do not grow and the solvent has the inhibition role (Black et al., 1991).

2.5 Solvent Properties

Table 2.2 shows the summaries of the physical properties of the ethanol and acetone as a solvent used for this study. From this table, there are several properties highlighted as an important properties used to done this research that is the molecular of each solvent, molar mass, density at specific temperature, and the molecular structure of the solvent.

Table 2.2 Solvent Properties

Properties	Ethanol	Acetone
Synonyms	Absolute alcohol Alcohol Drinking alcohol Ethyl alcohol Ethyl hydrate Ethyl hydroxide	Dimethyl ketone β-Ketopropane Propanone 2-Propanone Dimethyl formaldehyde Pyroacetic spirit (archaic)
Molecular formula	C_2H_6O	C_3H_6O
Molar mass	46.07 g mol^{-1}	58.08 g mol^{-1}
Appearance	Colourless liquid	Colourless liquid
Density	0.789 g/cm^3 (at 20°C)	0.791 g/cm^3
Melting point	−114 °C, 159 K, -173 °F	-95-93 °C, 178-180 K, -139--136 °F
Boiling point	78.37 °C, 352 K, 173 °F	56-57 °C, 329-330 K, 133-134 °F
Molecular structure (2D)		
Molecular structure (3D)		

(Source: http://www.wikipedia.org, 2012)

2.6 Radial distribution function

The Radial Distribution Function (RDF) is an effective way of describing the average structure of disordered molecular systems such as liquids, but it is also helpful when looking at disordered and ordered solids. One way in which we can analyse such structures effectively is to imagine how the average structure looks from the point of view of a single reference atom. Radial distribution functions can be determined both experimentally and from simulation, allowing direct comparison. In addition, all thermodynamic quantities can be derived from an RDF under the assumption of a pair-wise additive potential energy function (Gray et al, 1984).

The RDF has long been applied as a descriptor of the structure of liquids such as water and though they can be very computationally expensive to calculate, RDFs derived from large-scale molecular dynamics (MD) simulations have been useful in a wide range of applications (Kollman, 1991).

The pair potential gives information about the energy due to the interaction of a pair of molecules and is a function of the distance, *r* between their centers. Information about the structure or the distances between pairs of molecules is contained in the radial distribution function. For values of *r* less than those of the molecular diameter, *d*, goes to zero. This is consistent with the fact that two molecules cannot occupy the same space. From Figure 2.9 below, considering a homogeneous distribution of the atoms or molecules in space, the radial distribution function represents the probability to find an atom in a shell *dr* at the distance *r* of another atom chosen as reference point.

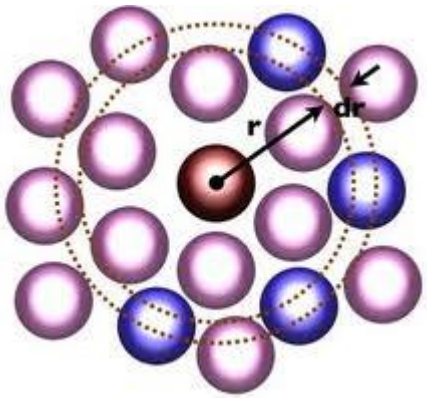


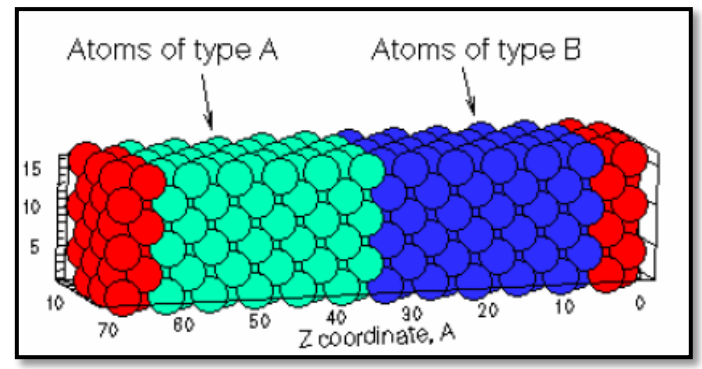
Figure 2.9 Space for the evaluation of radial distribution function.

(Source: http://www.wikipedia.org, 2012)

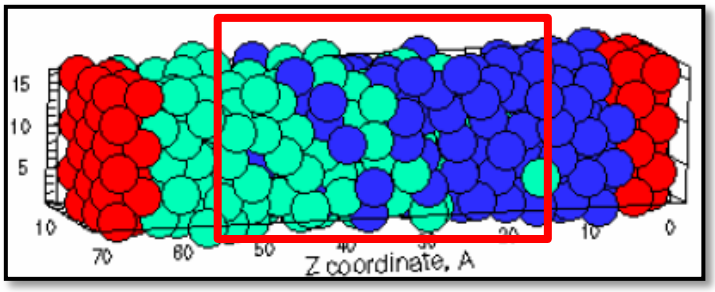
2.7 Diffusion

Diffusion is the transportation of matter from one point to another by thermal motion of atoms or molecules due to their phase such as fast in gas phase, slow in liquids phase, and very slow in solids phase. Diffusion very important in many processes as diverse in intermixing of gases and liquids, permeation of atoms or molecules through membranes, evaporation of liquids, drying of timber, doping silicon wafers to make semiconductor devices, and transport of thermal neutrons in nuclear power reactors (Cardona, 2000).

Figure 2.10 shows the schematic illustration of diffusions between solids. From the figure, we can see that how the atomic molecules interactions between each of the atoms and how diffusion really happens. In Figure 2.10 (a) the initial configuration of atoms type A and atom type B are separated each other into two different coordinate. After the simulation running, the diffusion occurs as shown in rectangular box in Figure 2.10 (b) after the mixing of atom A and atom B at specified times.



(a)



(b)

Figure 2.10 Schematic illustration of diffusion (Mark, 2003).

(Sources: Mark, 2003)

2.8 Active Pharmaceutical Ingredien

Active pharmaceutical ingredient (API) plays an important role in pharmaceutical development, manufacturing, and formulation. The solubility of an API in solvents and solvent mixtures has a considerable influence on the choice of solvents and the course of operation in solvent-based processes (Tu Lee, 2006).

Other than that, it is also an important element especially in drug development program which are subjected to the adulteration provisions of Section 501(a)(2)(B) of the Act, which requires all drugs to be manufactured in conformance with CGMP. Active Pharmaceutical Ingredients (API) of good quality are core to the manufacturing of effective and safe essential drugs. (Janet Bumpas, 2009).

In terms of definition, Active Pharmaceutical Ingredients (APIs) are the integral components of both the quality and the cost of pharmaceutical goods. Equality of access for developing country final formulators to high quality essential medicine APIs should be pursued as a public health goal. This requires looking at the API market from a sustainability and quality perspective as well as from a price perspective Bumpas. J., and Betsch. E. (2009).

2.9 Crystallizations

Many types of drug exist in the crystalline solid state that due to the stability and ease of handling during the various stages of drug development. Crystalline solids can exist in the form of solvates, polymorphs, or hydrates forms. Phase transitions such as polymorph interconversion, desolvation of solvate, conversion of crystalline to amorphous form and formation of hydrate may occur during various pharmaceutical processes, which may alter the dissolution rate and transport characteristics of the drug (Vippaguntaa, 2000).

Targeting of pure crystalline forms often requires expensive and time-consuming operations, such as repeated re-crystallization commonly carried out from organic solvents. Thus, the investigation of alternative methods, which permit the isolation of a particular crystalline form meeting flowability, compactability, solubility and bioavailability requirements, is of primary importance for the pharmaceutical industry (Bettini et al., 2001).

The degree of crystallinity or fraction of crystalline material was assessed by comparing the integrated area of the diffracted peaks of crystalline structures with the integrated intensity of the background peaks amorphous structures (Jenkins, 2000). The amorphous substances showed more background noise as they led to wider peaks with less intensity where the degree of crystallinity was calculated from the ratio of the total area under the curve after subtracting the background noise on the total area (Suryanarayanan and Mitchell, 1985).

Table 2.3 Crystal properties

Operating conditions			Polymorphic forms (%)				Degree of crystallinity	Diameter (μm)	
Pressure (bar)	Extraction temperature (^{0}C)		I	II	III	IV	(%)	Mean	Size distribution
Unprocessed starting material			-	-	100	-	89.1	84.64	[15.12-336.11]
170	35	75	-	-	100	-	68.6	0.97	[0.60–1.83]
170	55	75	-	71	29	-	57.9	1.21	[0.73–1.82]
200	75	75	2	71	24	3	75.4	1.51	[0.83–2.20]
240	35	75	-	-	100	-	64.4	1.14	[0.68–1.85]
240	35	75	12	18	70	-	58.6	1.27	[0.49–2.47]
240	40	85	6	74	20	-	44.9	0.91	[0.49–1.28]
240	60	85	4	76	20	-	42.1	0.80	[0.41–1.99]
240	100	135	9	59	17	15	57.4	0.85	[0.26–2.60]

(Sources: Gosselin, P., M., et al, 2002).

Table 2.3 shows the crystal properties, degree of crystallinity, size and size distribution of carbamazepine particles produced by the rapid expansion of supercritical solutions method under different operating conditions of pressure (bar), extraction temperature (◦C) and expansion temperature (◦C).

2.10 Fourier transforms infrared (FTIR) analysis

The concept of Fourier transform infrared (FTIR) spectroscopy has been known about more than a century. It began with the invention of the interferometer by Michelson in 1880s to measure the speed of the earth moves through the ether (the medium in which light travels). By measuring the interference between light

paths at right angles, one could find the direction & speed of the ether. Lord Rayleigh proposed that interference pattern produced by the interferometer that could be converted into a spectrum using Fourier transformation that has been found on that time. Take time around 60 year for FTIR spectroscopy to gain recognition as potent analytical tool (Martin, nd). The Michelson interferometer advantages were well-known, but considerable technical difficulties had to be overcome before a commercial instrument could be built. An electronic computer was needed to perform the required Fourier transform and this only became practicable with the advent of mini-computers, such as the PDP-8 which became available in 1965 (Griffiths and Hasseth, 2007).

Infrared radiation is a relatively low energy light which is the temperature of the object will affect the wavelength of the infrared radiation and it is known as black body radiation. The source temperature should be as high as possible in order to gain the maximize results. The choosing of an IR source needs some consideration. First, the material should be thermodynamically stable to prevent from break down and need replacing. This would obviously be an expensive and undesired approach. There is also the possibility that the source may produce an excess of IR radiation. This would saturate the detector and possibly over load the analog-to-digital converter (Rossini, 2007).

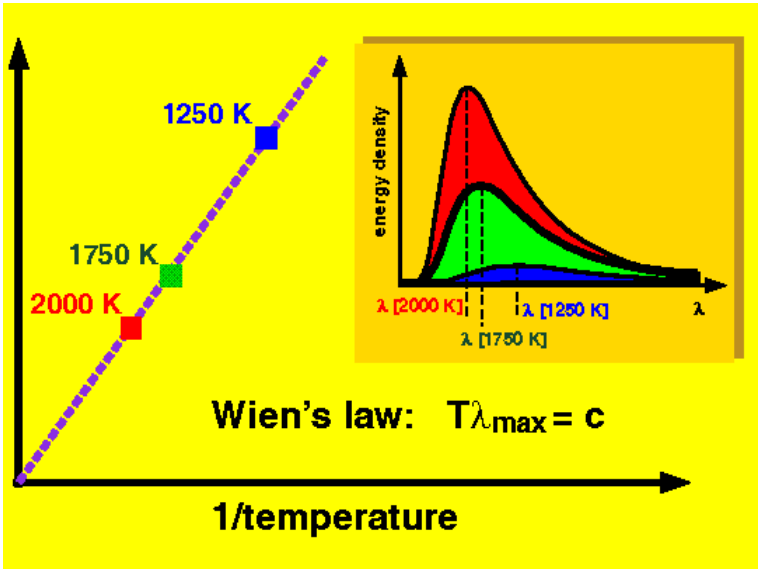


Figure 2.11 Effect of temperature in IR radiation

(Source: http://www.wikipedia.org, 2012)

Figure 2.11 shows the effect of temperature in IR radiation in FTIR analysis. As the 1/temperature increases the IR radiation also increases or can be said as IR radiation increase linearly as 1/temperature increases

CHAPTER 3

METHODOLOGY

3.1 Simulation Work

The MD simulation was carried out using the Material Studio software Version 5.5 utilizing HP Z400 workstation. The method of the MD simulation applied in this research was the same employed in earlier study of 2,6-DHB in toluene and chloroform solvent simulation (F. Adam et al). The single molecules of solvent ethanol were optimized and minimized using the generic COMPASS force field in Material Studio. Single molecular geometry was optimized to get the most stable configuration of molecule structure with lowest possible potential energy. Force field was chosen to run this simulation because of its high accuracy and is reported to be the most suitable for almost all organic structure (Sun, 1998). The simulation boxes of pure and binary systems were created as a periodic boundary condition that is equivalent to consider an infinite, space filling array of identical copies of the simulation region (Rapaport, 2004). The created cubical boxes contain number of molecules by 300 solvent which is pure ethanol that was created by

Amorphous Cell in Material Studio. The same way was applied to construct the cubical boxes of Carbamazepine in ethanol containing 100 molecules of Carbamazepine and 300 pure ethanol solvent. The energy minimization of simulation was applied in the cubical boxes. The boxes were equilibrated using Forcite Module by performing the molecular dynamics simulation in NVE ensemble for 200ps and followed by NPT ensemble for 500ps with the total of 700ps simulation time. Initially, the simulation was run under constant number of moles, volume and energy (NVE) to equilibrate the system at 1 atm and 298K. Next, the simulation was run under constant number of moles, pressure and temperature (NPT) using 1fs step size up to 700ps to represent the extraction process condition. For the dynamics run in the NVE ensemble, the temperature and pressure of the system is scaled down until the values achieved are consistent with the setting conditions in order to get a reasonable total energy for the system. Besides, dynamics run in the NPT ensemble will maintain the temperature and pressure of the system and control the simulation box size to achieve the density of the real system. Once the temperature, pressure and energy of the system were in equilibrium at the desired values, the radial distribution function of the systems were calculated and analysed from the trajectory files. For analysing, cut off for half of A length with 0.5 interval were chosen to perform the trajectory files. The radial distribution function depends on the density and temperature. Therefore, it is serves as an indicator of the nature of phase assumed by the simulated system. The hydrogen bonding strength was measured to describe the solvation strength of the solvent molecules towards the solute molecule through the calculation of the radial distribution function [rdf] (Suchocki, 2000). The radial distribution functions or structural property can be correlated to the probability of finding the nearest neighbour atom.

The strength of hydrogen bonding also can reflect the solvation and mass transfer behaviour in the extraction of CBZ in ethanol system. The mass transfer can be measured through the calculation of diffusion coefficient of solute and solvent molecule from the trajectory history.

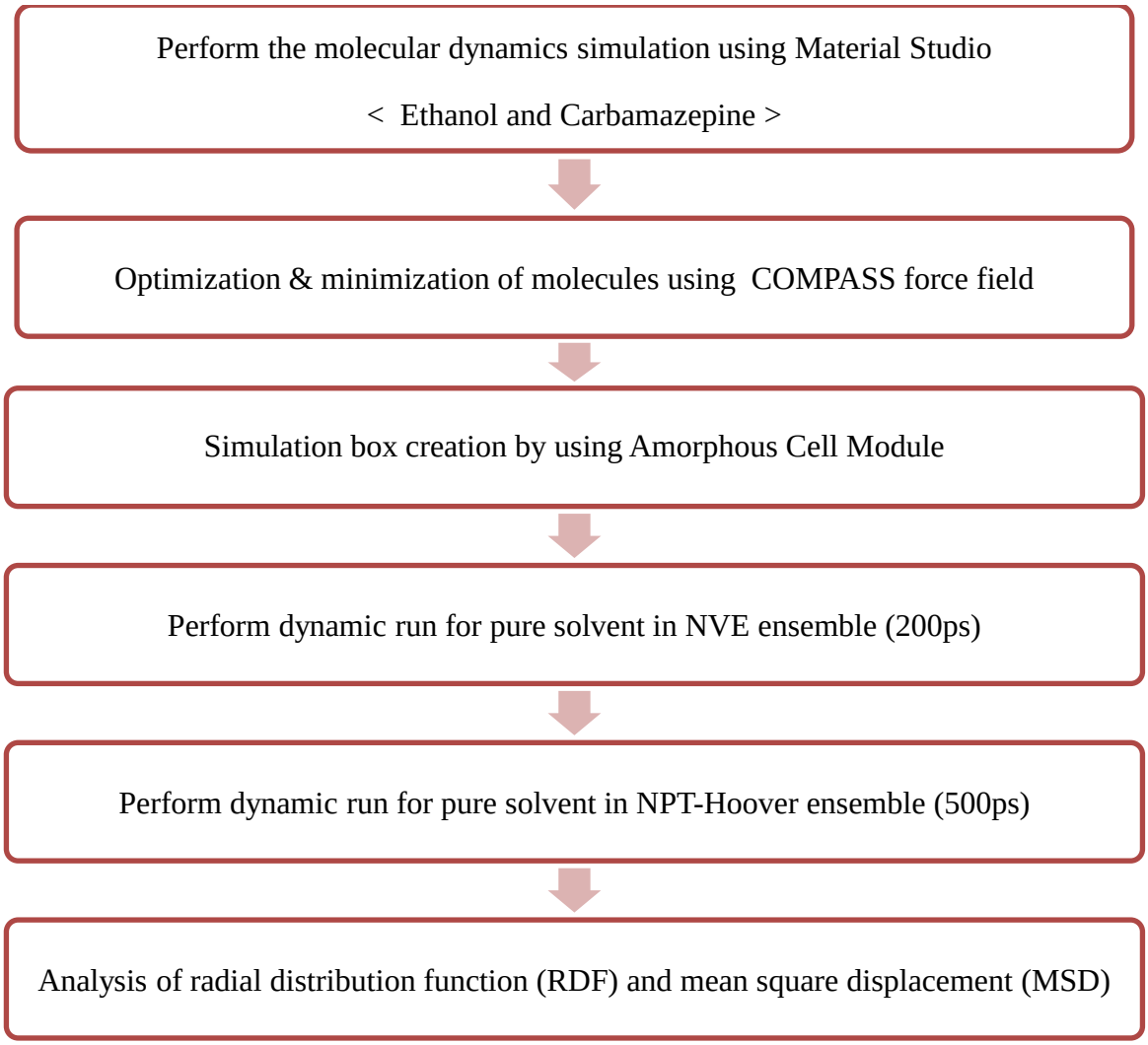
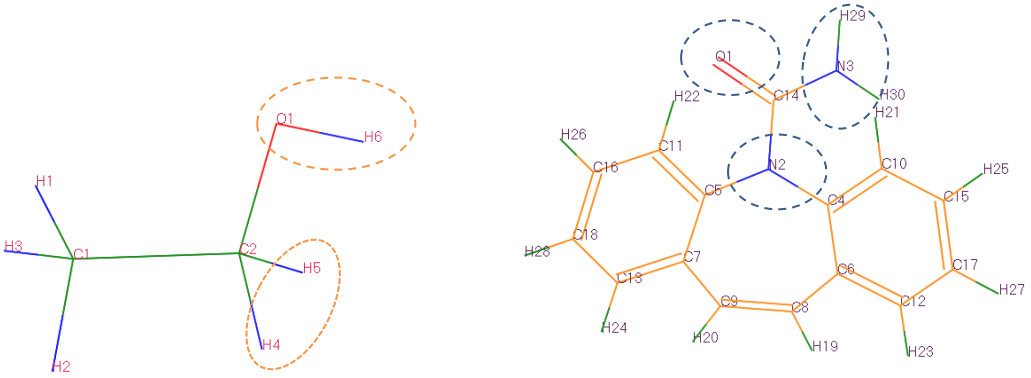


Figure 3.1 Process flowcharts for the molecular dynamics simulation procedures.

Figure 3.1 shows the summarise of the simulation process along this research starts with perform the molecular dynamics simulation of ethanol and carbamazepine using the Material Studio followed by optimization and minimization of molecules using COMPASS force field, box creation by Amorphous Cell Module, perform dynamic run for pure and binary and lastly analysis the rdf and mean square displacement.

3.2 Molecular Labeling

From the Figure 3.1 below, the molecular structures were labeled by naming every single atom in the molecules. It is because all the atoms play a significant role in the polymorphism of CBZ based on their ability to form hydrogen bonding with particular neighbouring atoms in the solution system. The label for CBZ structure was adopted from the previous MD study in order to facilitate in performing the comparison between this researches with the previous one.



(a) Ethanol (b) Carbamazepine

Figure 3.2 Molecular structure defining the atomic numbering

Table 3.1 Molecular dynamics simulation details for pure ethanol using COMPASS force field.

System	Ethanol
Number of molecules	300
NVE (ps)	200
NPT (ps)	500
Simulation time (ps)	700
Timesteps (fs)	1
Cut off (Å)	15.325
Interval (Å)	0.5
Simulated density (g/cm^3)	0.785
Measured density (g/cm^3)	0.789

Table 3.2 Molecular dynamic simulation details for Carbamazepine in ethanol mixtures using COMPASS force field.

System	Ethanol mixture
Number of solute molecules	100
Number of solvent molecules	300
Equilibration time in NVE ensemble (ps)	200
Equilibration time in NPT ensemble (ps)	113
Total simulation time (ps)	313
Timestep (fs)	1
Cutoff (Å)	15.325
Interval (Å)	0.5
$\rho_{simulated}$ (g/cm^3)	1.038
$\rho_{theoretical}$ (g/cm^3)	1.048

3.3 Experimental Section

Gravimetric method was used in this experiment to determine the solubility of the carbamazepine. The solubility of Carbamazepine, (5H-dibenz(b,f)-azepine-5-carboxamide) was synthesized by mixed or diluted this types of drug with different types of solvents, hydrogen donor or known as polar solvent and dipolar aprotic solvent (Mirmehrabi and Rohani, 2004). For this experiment, we used ethanol as hydrogen donor solvent and acetone as dipolar aprotic solvent at constant room temperature and pressure. The adequate amount of solvent was measured using pipette, 3 mL for ethanol and acetone solvents. Boiling tube of known mass is used to fit into the thermal block of thermo mixer. Carbamazepine samples are prepared by weighing out the desired amount of carbamazepine predicted from the literature and then poured into the prepared solvent. More solute is added until excess appeared. The boiling tube is mounted in the thermal block for stirring at specific temperature for one hour at which the samples were visually inspected to ensure complete dissolution before undergo the Fourier transform infrared (FTIR) analysis. More known amount of carbamazepine will be add if the all the excess carbamazepine solute completely. The mass of the solute used is 0.1102g for ethanol and 01.267g for acetone which showed different amount of solute used for different solvents. The speed of the mixer was set around 300-400rpm. The stirring is continued for another three hour to ensure complete mixing for supernatant to form. The diagram of the FTIR and thermo mixer used was shown in Figure 3.3 and Figure 3.4 with complete labeled.

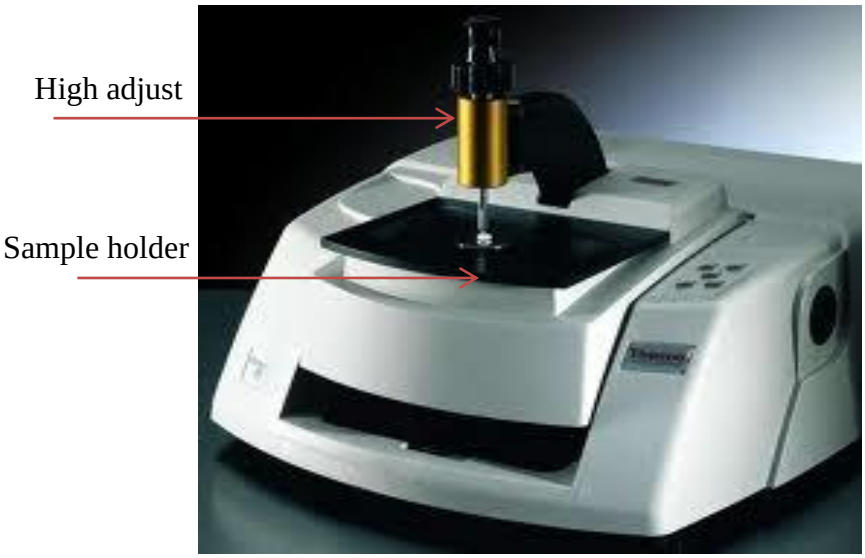


Figure 3.3 Fourier transform infrared (FTIR)

:

Figure 3.4 Thermo mixer

CHAPTER 4

RESULT AND DISCUSSION

4.1 Simulation Data

Table 3.1, showed the simulated density of pure ethanol which is acceptable and in agreement with the experimentally determined values. The measured density of the pure ethanol is 0.789 g/cm^3 while the density of the ethanol after simulation run was 0.785 g/cm^3 which shows a slightly different with 0.51% percentage different by using COMPASS force field.

While Table 3.2 summaries that the simulated densities calculated for those solvents mixtures at constant concentration are in good agreement to the theoretical densities values of 1.048 g/cm^3 and 1.038 g/cm^3 simulated densities. The simulated density absolute error is around 0.95% from the setting value in the ethanol mixture.

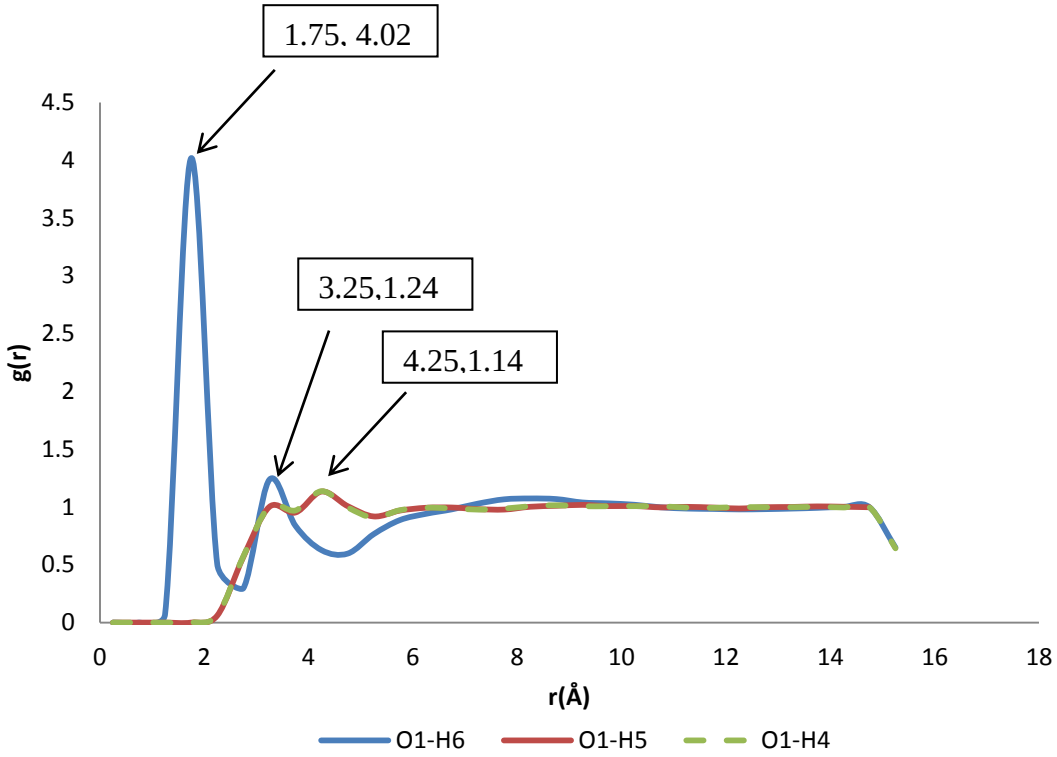
The diffusion coefficient and radial distribution function of the systems were calculated and analysed based on the trajectory files obtained along this research. For

radial distribution function, the intermolecular forces are studied for solute-solvent and solvent-solvent interaction. The intermolecular forces of pure system for ethanol are analysed to have the comparison with the previous study by using different types of force field to ensure the rdf obtained from this research is in good agreement with those finding. The results obtained from this research indicate that the character of the intermolecular interaction played an important role in the crystallization process in solution.

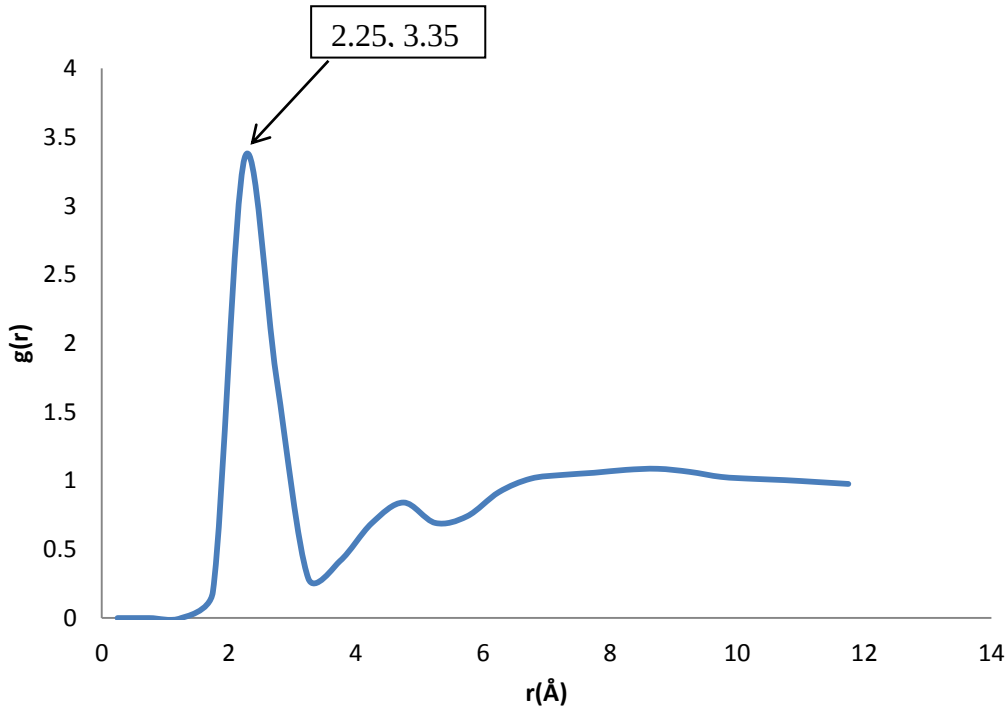
4.2 Pure System

In pure ethanol, H-bond occurs between O1---H6 at 1.75 Å. Figure 4.1 (a) shows the first peak represents the nearest neighbour interaction between the specific types of atoms in the liquid solution. From the rdf pattern, it shows that the strong interaction occurs between O1---H6 atoms in the pure ethanol solution due to strong attraction forces atom O1 and H4 to form hydrogen bond. While for the rest of atoms which are between O1---H5 and O1---H4 the interaction between molecules is still happen but the distance is greater compared to the O1---H6. O1---H5 and O1---H4 shows the same distance value of 4.25 Å. Figure 4.1 (b) shows the H6---H6 repulsion between ethanol solvent-solvent which give the distance 2.25 Å which means the interaction between H6---H6 in ethanol solvent is at moderate if want to compared with O1---H6 and O1---O1 distance.

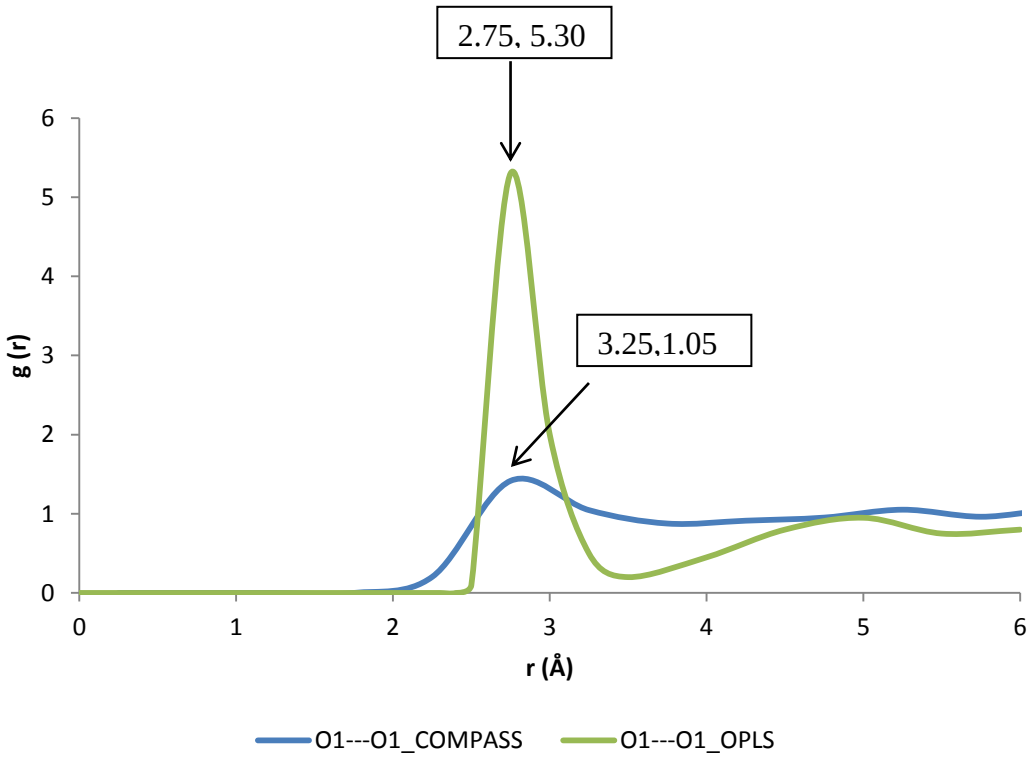
The pure liquid ethanol structure result from this simulation work, have been validated by comparing the generated radial distribution function (rdf) from Saiz et al (1996) simulation work using OPLS (Optimised Potential Liquid Structure) force field. Figure 4.1(c) compares the hydrogen bonding interaction of O1---O1 by different system. In figure 4.1 (c), the rdf trend using COMPASS force field has a better pattern compared to OPLS force field with two broad peaks which should suggest the longer simulation time as well to obtain the sharp peak as revealed in Saiz et al (1996) work.



(a)



(b)



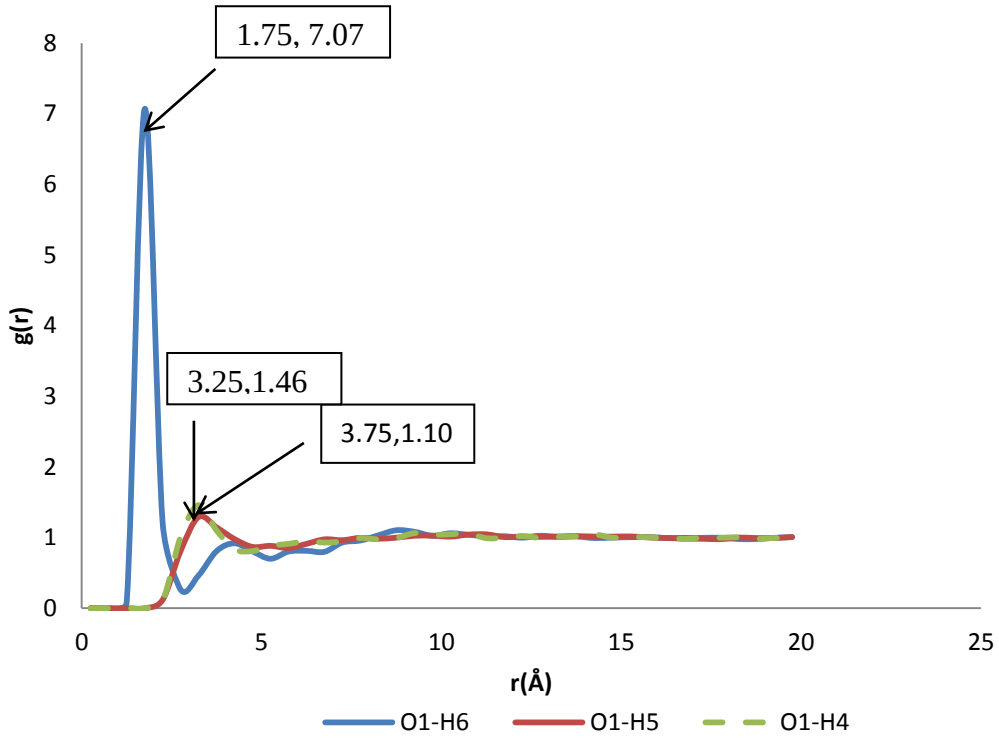
(c)

Figure 4.1 Radial distribution function of pure methanol: (a) O1---H interaction; (b) H6---H6 interaction; (c) Comparison of O1--- O1 in pure ethanol liquid system from this study and Saiz et al (1996) work using COMPASS and OPLS force field respectively.

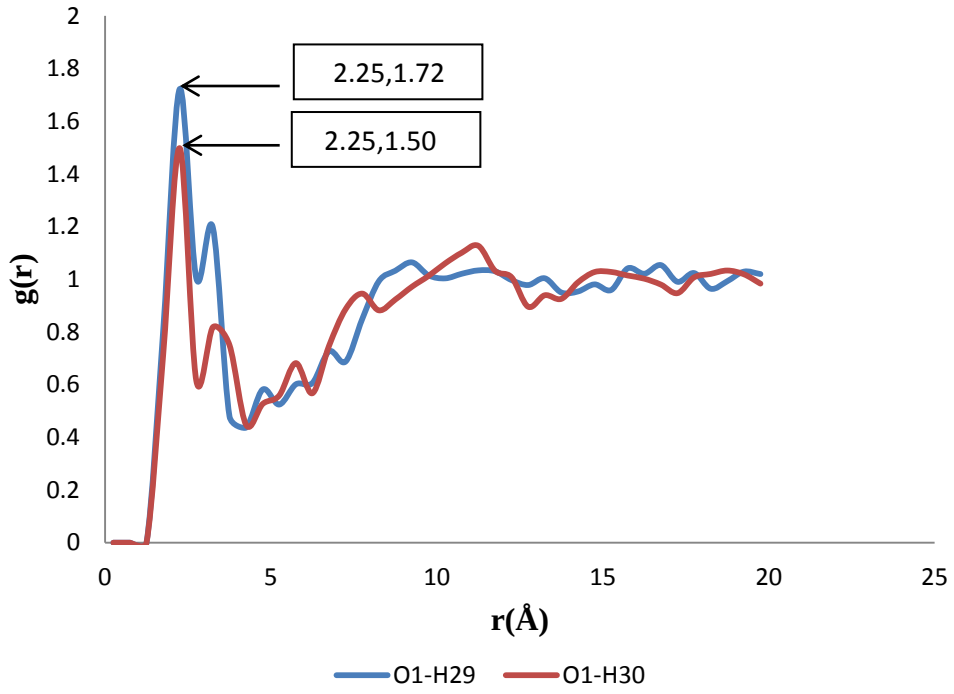
4.3 Solute-solvent interaction

In the binary system, the hydrogen bond plays an important role in affecting the mass transfer (Suchoki, 2000) of CBZ molecule during the extraction process. The different degree of hydrogen bonding between the solute-solvent will affect to the diffusion rate of solute molecule. From figure 4.2 (a) O1---H6, O1---H5, O1---H4 represents the hydrogen bonding between solute-solvent as illustrated in Figure 4.1 (a). In comparison, O1---H6 play a significant role compared to O1---H5 and O1---H4 intermolecular interaction to increase the mass transfer rate because of stronger interaction from the rdf peak O1---H6 has a first neighbor atom at 1.75 Å compared to O1---H5 at 3.75 Å and O1---H4 at 3.25 Å. The g(r) of O1---H6 solute-solvent interaction is higher compared to pure system was because of the higher formation of H-bond formed after diffusion. Figure 4.2 (b) shows the interaction between O1---H29 and O1---H30 have the same distance at 2.25 Å. Weak H-bond was formed between the nitrogen atom from CBZ with hydrogen from ethanol as shown in figure 4.2 (c) due to less electronegative compared to oxygen and figure 4.2 (d) shows the interaction between O1---O1 from CBZ and ethanol with distance 2.75 Å.

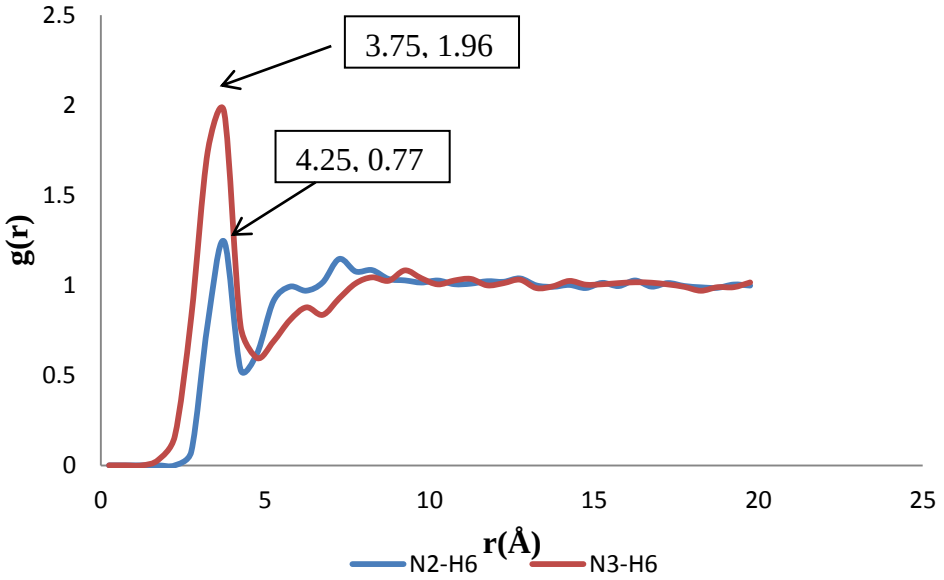
The functional group of CBZ plays an important role in forming hydrogen bonding with other neighbouring molecules. Depending on the types of solvent, CBZ can produce the desired polymorph by choosing the appropriate solvent since it has a strong influence on the crystal polymorph. From this study ethanol will conduct strong intermolecular interaction to CBZ atoms. From the discussion above, it is clearly shows that ethanol solvent use in crystallizing process of CBZ may lead to polymorphism.


1.75, 7.07
3.25,1.46
3.75,1.10
g(r)
r(Å)
O1-H6
O1-H5
O1-H4

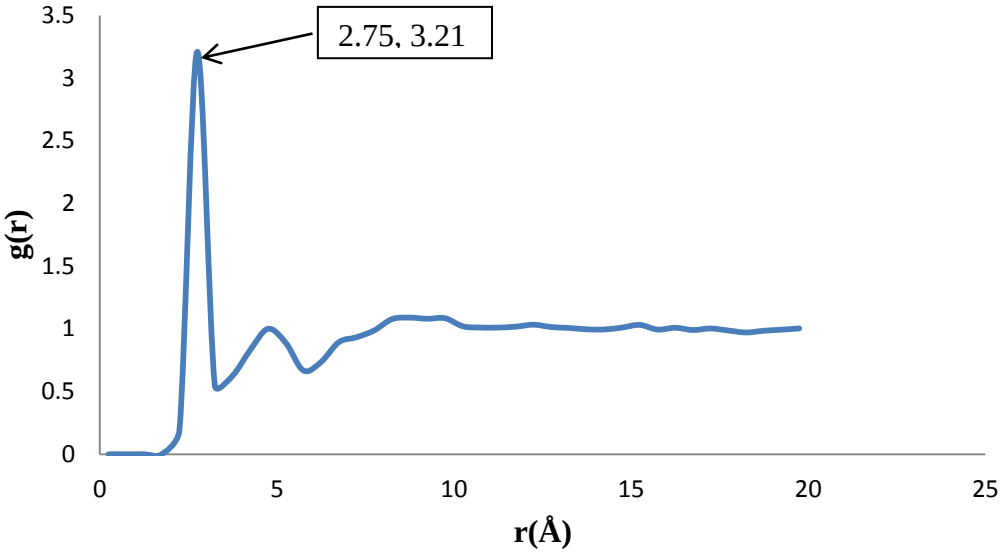
(a)


2.25,1.72
2.25,1.50
g(r)
r(Å)
O1-H29
O1-H30

(b)



(c)

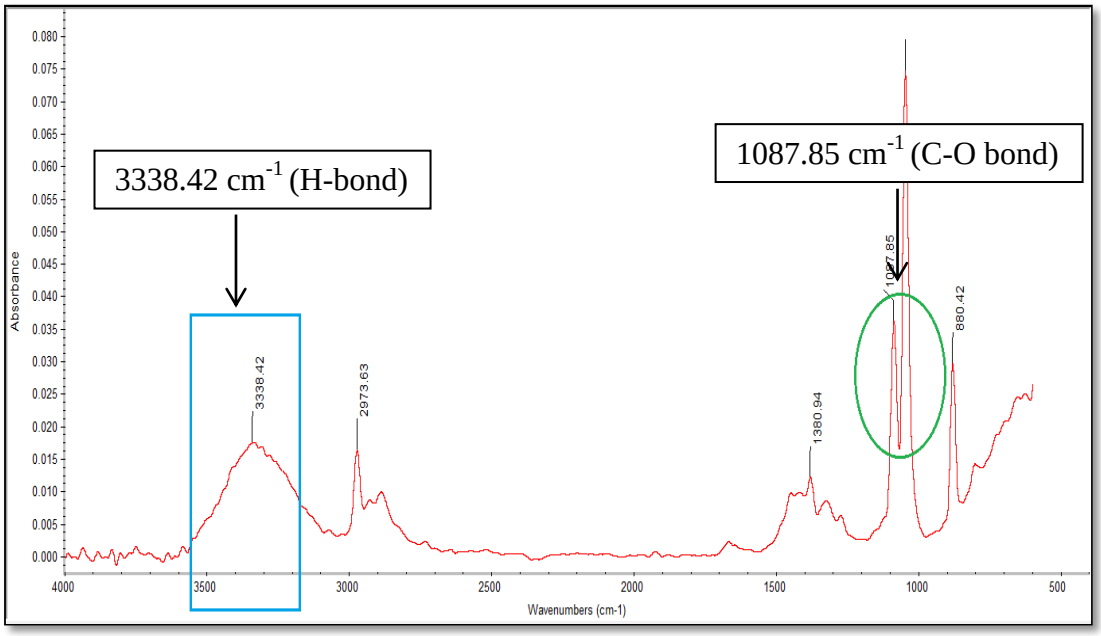


(d)

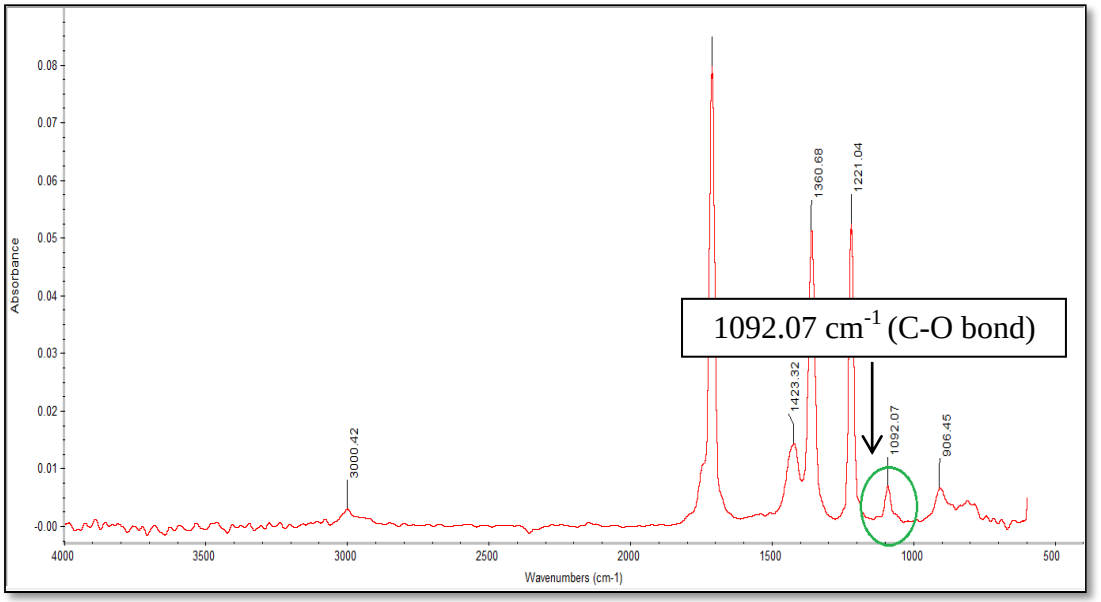
Figure 4.2 Radial distribution function of binary mixture ethanol and carbamazepine: (a) O1 CBZ ---H Ethanol interaction; (b) O1 Ethanol ---H CBZ interaction; (c) N---H6 interaction; (d) O1---O1 interaction for Ethanol and CBZ.

4.4 Experiment Data

Figure 4.3 showed the FTIR spectra for pure solvent ethanol and acetone. From figure 4.3 (a) the blue rectangular represent the existence of the H-bond in ethanol with wavelength value of 3338.42 cm^{-1}. The different height of the peak showed different bond exists in this solvent. The green circle with 1087.85 cm^{-1} wavelength represented the existence of the strong C-O bond in ethanol. H-bond exist when the reading of the wavelength is between 3200-3600 cm^{-1} (Basseler et al., 1981). Figure 4.3 (b) showed the absence of the H-bond. It is because acetone contained the double bond oxygen (C=O) which cannot donate hydrogen for bonding but only can be act as acceptor. The green circle showed the existence of the C-O bond in acetone with 1092.07 cm^{-1} wavenumber.



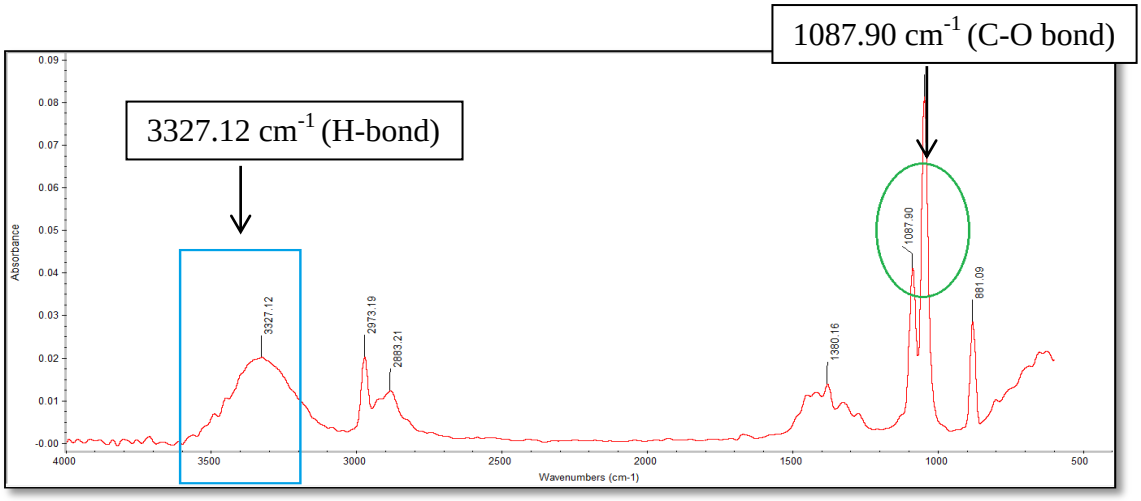
(a)



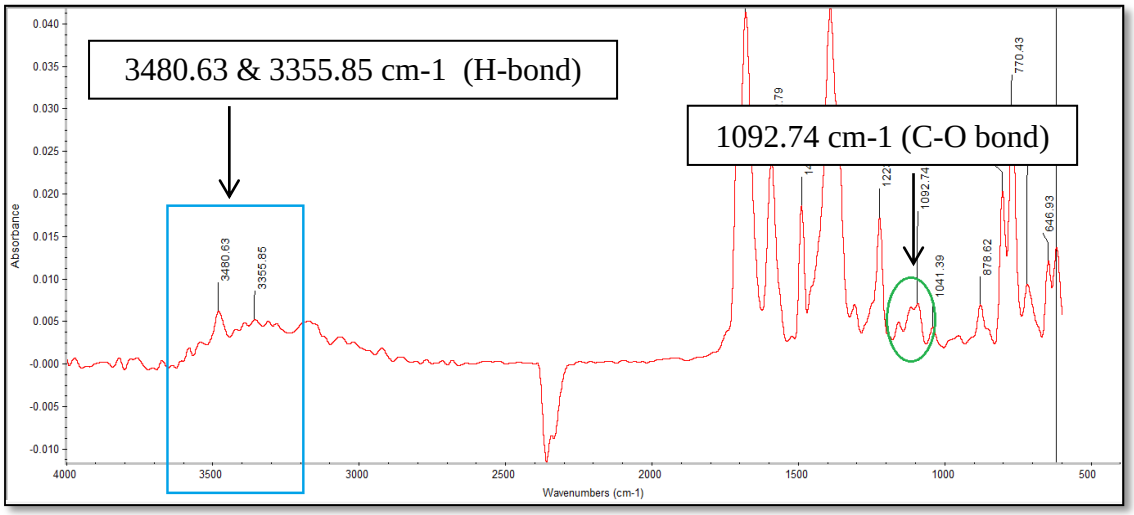
(b)

Figure 4.3 FTIR analysis spectra: (a) pure ethanol; (b) pure acetone.

Figure 4.4 showed the FTIR spectra for binary solution. From figure 4.4 (a) which is the FTIR spectra for CBZ-ethanol mixture, the H-bond exist at 3327.12 cm-1 wavenumber and the C-O bond exist at 1087.90 cm-1. For mixture CBZ-acetone, the H-bond exist at two peak 3480.63 cm-1 and 3355.85 cm-1 wavenumber which is showed in blue rectangular and the existence of the C-O bond was shown in green circle which is 1092.74 cm-1 wavenumber.



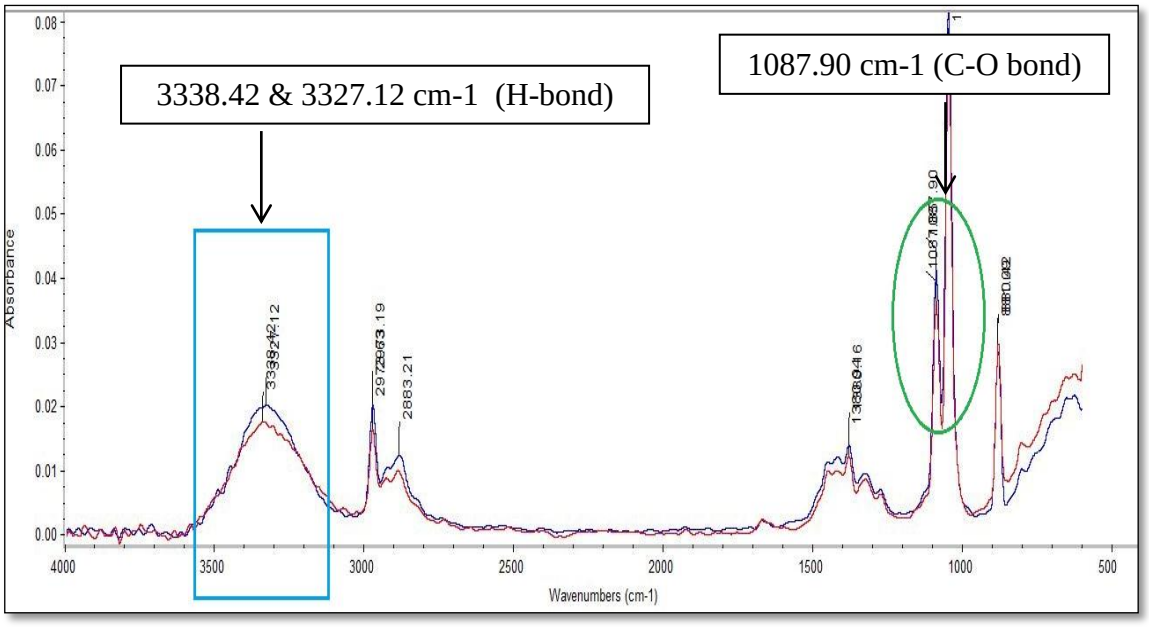
(a)



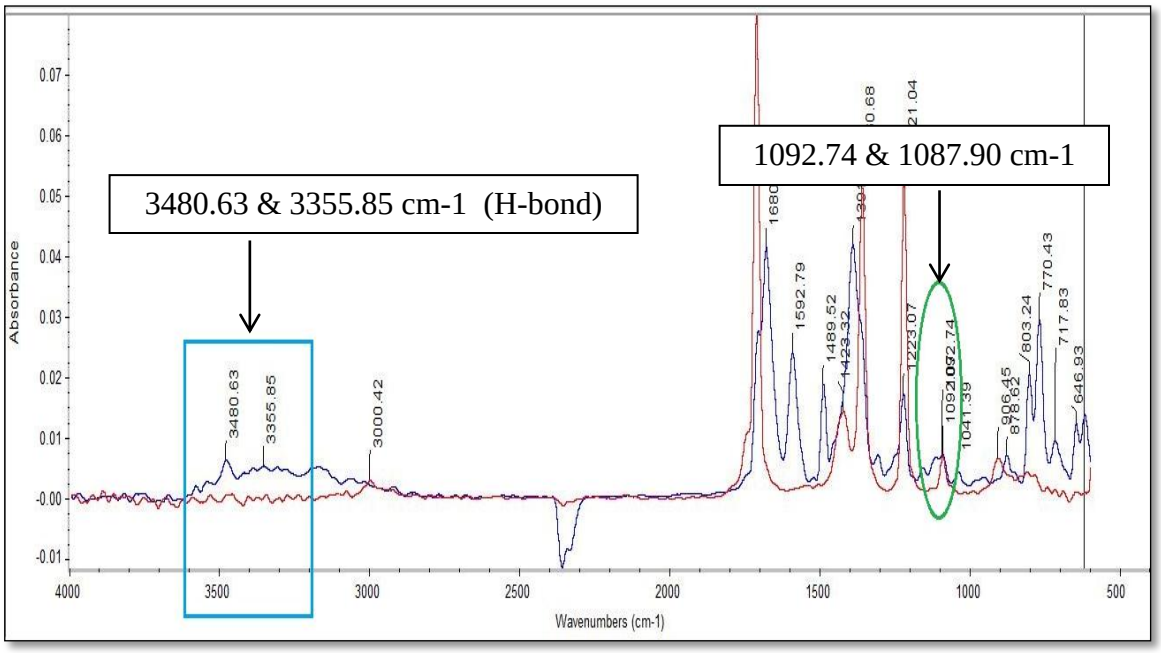
(b)

Figure 4.4 FTIR analysis spectra: (a) CBZ-ethanol mixture; (b) CBZ-acetone mixture.

Figure 4.5 showed the overlapping of spectrum for pure ethanol with binary ethanol and pure acetone with binary acetone. Based on the figure above, the peak height and the absorbance is varies at different wavenumber. The ranged of the spectra are between 4000 cm^{-1} to 500 cm^{-1} but there are no significant values from 3000 to 1000 of wavelength. For figure 4.5 (a) the existence of the H-bond can be seen in the blue rectangular box which is the peak of the spectra slightly increases at the wavenumber of 3338.42 cm^{-1} and 3327.12 cm^{-1} and the presence of the C-O bond can be seen in the green circle for both component. The presence of the H-bond for figure 4.5 (b) can be seen between the wavenumber 3480.63 cm^{-1} and 3355.85 cm^{-1} compare to pure acetone which is no H-bond exist as shown in blue rectangular box.



(a)



(b)

Figure 4.5 FTIR analysis spectra: (a) pure ethanol and CBZ-ethanol mixture; (b) pure acetone and CBZ-acetone mixture.

Pure solvent
Mixture

Figure 4.6 showed the comparison FTIR analysis spectra for CBZ-ethanol mixture and CBZ-acetone mixture. From the figure, we can see that the most H-bond form exist when CBZ diluted with the ethanol which is can be seen from the height of the peak in the blue rectangular box. The peak of the CBZ-ethanol mixture is more height compared to CBZ-acetone mixture because the oxygen atoms of the ethanol easy to attracted to hydrogen atom from CBZ to form H-bond compared to acetone which consist double bond.

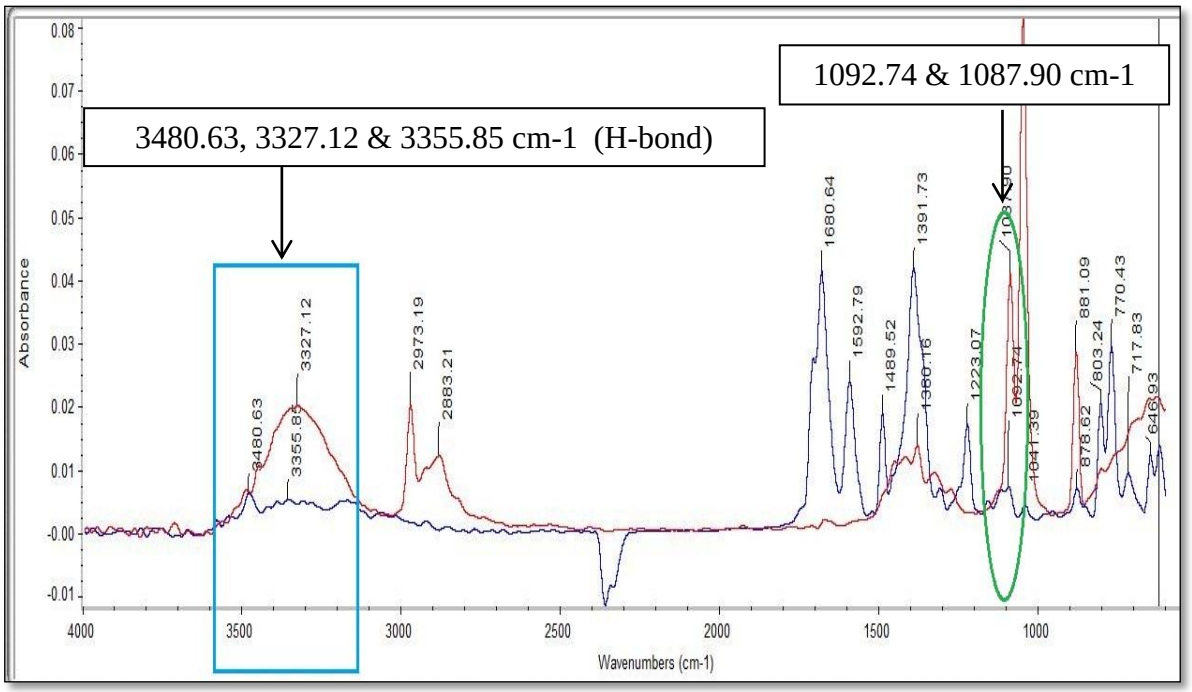


Figure 4.6 Comparison FTIR analysis spectra for CBZ-ethanol mixture and CBZ-acetone mixture.

CBZ-ethanol mixture
CBZ-acetone mixture

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

5.1 Conclusions

In this study, the affect of the types of solvent plays an important role in determining the types of crystal polymorph forms which will affect the stability of the product. The use of simulation especially in pharmaceutical industry will helps the researcher in doing the research in short time and low cost because they don't have to set up the real experiment and just need to create the model like the real process or system in computer in order to achieve their objective while run the experiment by simulation. The result from the simulation shows that the interaction and distance between atoms plays the main role in the formation of the H-bond and the diffusion coefficient of the mixture. From the experimental result analysis, there is difference in the intermolecular interaction behavior and the formation of the H-bond between the solute of CBZ depending on the solvents used such as ethanol and acetone. From experimental ethanol shows the strong formation H-bond same as what simulation result shows.

5.2 Recommendations for Future Research

From this study, there is a few problems that occur such as we cannot isolate the solute and solvent molecules as their have same atom label and those problems influence our result for the rdf analysis. For experimental section, the mixture rapidly turns to crystal form due to temperature effect and specific place should be provide in order to have the accurate results. Therefore, as a suggestion for future research, make sure that the solute and solvent can be isolated first before running the experiment. Besides, the calculated rdf from this study is not in good agreement with the previous study. As a recommendation, the simulation should be run for a longer time for the molecules to achieve its equilibrium state and use different method analysis such as TGA, XRD, DSC, and morphology.

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APPENDIX A

SNAPSHOTS FROM SIMULATION

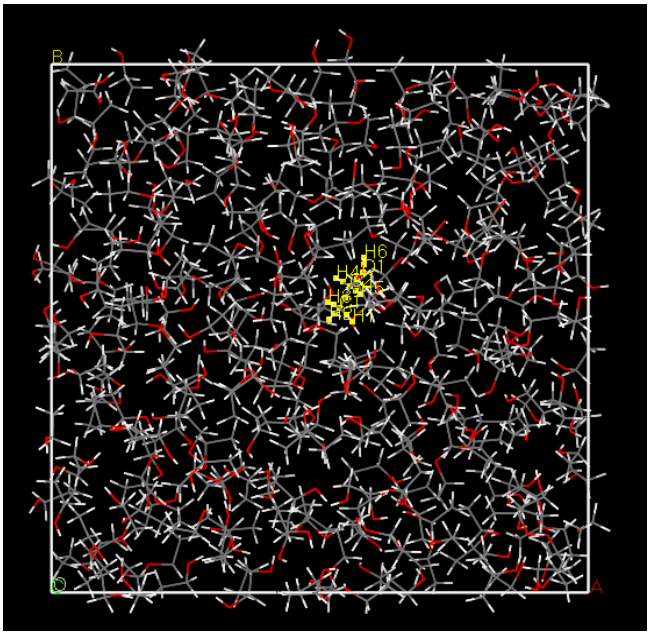

Figure A.1 Pure ethanol

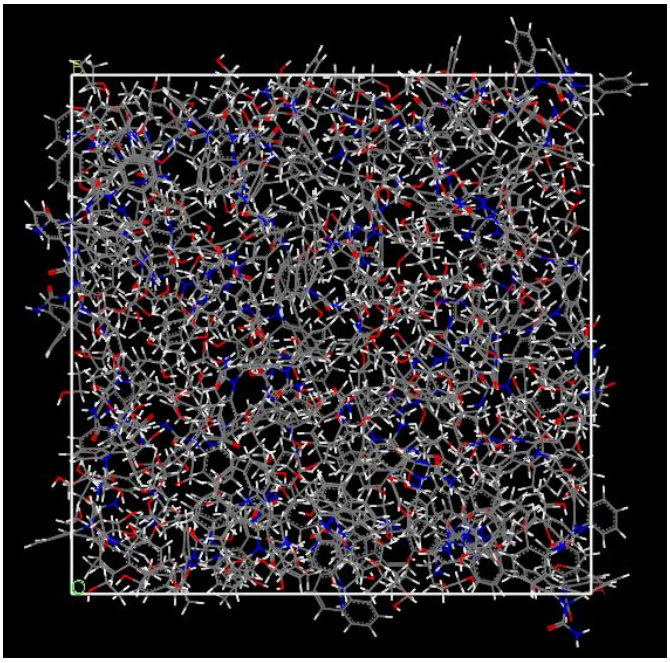

Figure A.2 Ethanol and Carbamazepine mixture

Table A.1 CHARACTERISTIC INFRARED ABSORPTION FREQUENCIES

Functional Group	Type of Vibration	Characteristic Absorptions (cm-1)	Intensity
Alcohol			
O-H	(stretch, H-bonded)	3200-3600	strong, broad
O-H	(stretch, free)	3500-3700	strong, sharp
C-O	(stretch)	1050-1150	strong
Alkane			
C-H	stretch	2850-3000	strong
-C-H	bending	1350-1480	variable
Alkene			
=C-H	stretch	3010-3100	medium
=C-H	bending	675-1000	strong
C=C	stretch	1620-1680	variable
Alkyne			
C-H	stretch	3300	strong,sharp
−C≡C−	stretch	2100-2260	variable, not present in symmetrical alkynes
Aromatic			
C-H	stretch	3000-3100	medium
C=C	stretch	1400-1600	medium-weak, multiple bands
Analysis of C-H out-of-plane bending can often distinguish substitution patterns			
Carbonyl			
C=O	stretch	1670-1820	strong
(conjugation moves absorptions to lower wave numbers)			
Ether			
C-O	stretch	1000-1300 (1070-1150)	strong
Nitrile			
CN	stretch	2210-2260	medium